UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/099,895	03/14/2002	Mark Andrew Guthridge	3991/0K379US0	5422

7590 05/17/2005

DARBY & DARBY P.C.
805 Third Avenue
New York, NY 10022

EXAMINER	
HOWARD, ZACHARY C	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 05/17/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/099,895	GUTHRIDGE ET AL.	
	Examiner	Art Unit	
	Zachary C. Howard	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) *1-20,23 and 25-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21,22 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/14/02; 10/6/03; 4/26/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

RD

DETAILED ACTION

Advisory Information

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825). **The instant specification will need to be amended so that it complies with 37 C.F.R. § 1.821(d) which requires a reference to a particular sequence identifier (SEQ ID NO:) be made in the specification and claims wherever a reference is made to that sequence.** See M.P.E.P. 2422.04.

The instant specification and claims contain numerous references to particular sequences that are not identified by a sequence identifier (SEQ ID NO:). Applicants must amend the specification and claims so that each amino acid sequence of four or more amino acids, and each nucleotide sequence of ten or more nucleotides and any reference to a particular residue in such a sequence, is identified by sequence identifier.

The following claims contain references to sequences, but are not in compliance with 37 C.F.R. § 1.821(d) and must be amended to include a reference to a particular SEQ ID number:

Claims 2 and 16 - "...position 585 of the common β_c according to Figure 1"

Claim 8 - each of the twenty-seven recited amino acid sequences

Claim 9 - "...HSRLP corresponding to amino acids 582 to 587..."

Claim 10 - each reference to specific residues in specific sequences

Claims 13 and 14 – ^{582}HRSLP^{587} and Ser^{585}

Applicant's cooperation is requested in correcting any other sequence references in the specification or claims that do not include a sequence identifier, and that applicant becomes aware of.

Election/Restrictions

Applicant's election with traverse of Group IV, claims 21, 22, 24 and 25, in the reply filed on 2/14/2005 is acknowledged.

The traversal is on the ground(s) that Group I (claims 1-14) and Group IV (claims 21, 22, 24, and 25) are a product and a process of use that "do not warrant separate search and examination", that "represent a web of knowledge and continuity of effort that merits examination in a single application", and that search of the subject matter of Group IV will necessarily require a search of subject matter of Group I.

This is not found persuasive because under current examination guidelines, the examiner may require restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. In this instant application, Applicants have elected the process claims (Group IV). The product claimed in the product claims (Group I) will be examined in so far as it is required to examine the process claims.

The requirement is still deemed proper and is therefore made FINAL.

The examiner notes that in the restriction requirement mailed 10/14/2004, claim 25 was improperly placed with Group IV. Claim 25 depends from claim 23, and is drawn to the same invention (a method of binding a cytoplasmic protein to a receptor) as claim 23, and therefore should properly be placed in the same Group (III) with claim 23. Therefore, claim 25 is now placed with Group III and shall treated as such.

Claims 1-20, 23, 25 and 26-28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Applicant's election of cell survival as the species of cellular activity in the reply filed on 2/14/2005 is acknowledged.

All of the elected claims read on the elected species.

Claims 21, 22 and 24 are under consideration.

Specification

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The current title "Binding motif of a receptor " is not descriptive because the elected claims are directed only to a method of activating cellular activities.

The following title is suggested: "Method of activating cellular activities".

Claim Objections

Claims 21, 22, and 24 are objected to because the claims encompass are dependent on claim 1, which is a non-elected invention. Appropriate correction is required.

Claims 21, 22, and 24 are also objected to because the claims encompass non-elected inventions non-elected species. Appropriate correction is required.

Claim Rejections - 35 USC § 112, 1st paragraph, enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21, 22 and 24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of stimulating hematopoietic cell survival by regulating phosphorylation of a β_c chain, does not reasonably provide enablement for a method of activating or regulating cellular activities by regulating phosphorylation of a binding motif of a receptor or a functional equivalent or analogue thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claims are directed to a broad genus of methods of activating cellular activities by 1) regulating the phosphorylation of a binding motif of a receptor containing a serine residue and 2) subjecting the binding motif to a cytoplasmic protein wherein said cytoplasmic protein is associated with cellular activities.

The specification teaches expression of two subunits (the α and β_c chains) of the IL-3 receptor in a CTL-EN mouse cell line. The specification further teaches "while IL-3 was able to promote viability of the CTL-EN cells expressing wtβ_c [wild type β_c chain] for up to 3 days", cells expressing a mutant form of the β_c chain lacking the residue Serine-585 were reduced to 18% viability in three days. The specification teaches that this result (in view of the other results) demonstrates that cell survival of the CTL-EN cells in response to IL-3 requires phosphorylation of the Ser-585 residue. The specification does not demonstrate that this phosphorylation occurs for any other receptor or any other cell type. However, the β_c chain is shared in common with the GM-CSF and IL-5 receptors. Furthermore, based on sequence similarities to the β_c chain, the specification specifically contemplates (page 22-24) 21 other species of receptors in addition to GM-CSF/IL-3/IL-5 for which the claims can be practiced. However, the specification teaches (pg 18) that "the receptor may be any receptor that is capable of binding to an extracellular molecule or protein and which mediates its function through the binding of a cytoplasmic molecule or protein such as 14-3-3 protein. The specification (same page) also provides 11 examples of cellular activities that can be activated, including cell survival, proliferation, transformation, differentiation, mitogenesis, chemotaxis, motility, enhanced phagocytosis, bacterial killing, superoxide production and

cytotoxicity, but does not limit the definition of cellular activities to these embodiments. The specification does not limit the type of cell types that may be used in the invention, and therefore the method encompasses any cell type, such as bacterial, yeast, plant or animal cells.

The breadth of the claims is extreme because the claimed method encompasses a multitude of possible combinations of cell types, receptor types and cellular activities. Furthermore, the claims encompass the method as performed in vivo within an organism, or with cells in a culture, or in vitro in a cell-free environment.

It is noted that the prior art (Okuda et al, 1997, cited below) teaches methods of activating cellular survival that are encompassed by the claimed invention. The claims are enabled for a few, specific operative embodiments of the claimed invention, such as the method of activating cell survival taught in the specification described above, and the method of activating cell survival taught by Okuda described below, a skilled artisan would predict that the claims also encompass numerous inoperative combinations of cells, receptors, and cellular activities. In order to practice the full scope of the claimed method, a skilled artisan would need to engage in undue experimentation in order to identify these inoperative embodiments.

The claims encompass a method of activating cell survival as performed with the GM-CSF/IL-5/IL-3 receptors expressed in any cell type, for example, any type of bacterial, yeast, plant or animal cell. The specification does not teach whether or not the expression of this receptor in any cell type other than hematopoietic cells will promote cell survival. However, there are numerous types of cells, including bacterial, yeast, plant, and animal cells (such as HEK293) that do not undergo programmed death. Therefore, in order to practice the full scope of the claimed method, a skilled artisan would need to introduce the receptor in to each of these cell types and then test whether or not cell survival could be stimulated.

The claims also encompass a method of activating cell survival as performed with the GM-CSF/IL-5/IL-3 receptors in vitro in a cell-free system or with animal cells located within an organism. The claim encompasses host cells in an organism that naturally express said receptor, or cells genetically engineered to express the receptor,

e.g. transgenic organisms or recombinant cells expressing the receptor administered to an organism (gene therapy). The specification teaches that the βc chain of these receptors is phosphorylated and subjected to a 14-3-3 protein associated with cell survival in isolated cells. While this is interesting and worthy of further study, Applicant has not demonstrated that this phosphorylation, binding and associated cell survival would occur in a cell-free system or in cells located within an organism, and it is unpredictable whether or not under these conditions, which are substantially different from those taught by Applicants, and to which Applicants provide no guidance. Furthermore, there are no methods or working examples disclosed in the instant application for creating transgenic multicellular animals that express the receptor, and the unpredictability in the art of creating transgenic animals in very high.

The claims also encompass the method as performed with hematopoietic cells, but with any type of receptor to stimulate any type of cellular activity. While the specification provides examples of twenty-one other receptors that have potential binding motifs similar to the β_c chain, the specification does not teach the correspondence between any of these receptors and particular cellular activities. Because specific receptors are generally involved in specific cellular activities, a skilled artisan would predict that the claimed method would not be operative for a large number of combinations of receptors and cellular activities. In order to practice the claimed method over the full scope of the claim, one of ordinary skill in the art would to engage to introduce each receptor into hematopoietic cells and test each type of cellular activity to determine whether or not that receptor could be used to activate each particular claimed cellular activity. Furthermore, even if a particular receptor can be used to activate a particular cellular activity, the claim requires that the binding motif of the receptor is phosphorylated and subjected to a cytoplasmic protein that is associated with the cellular activity. However, the claims encompass many inoperative embodiments. For example, the specification (Example 8) teaches that "association of 14-3-3 with β_c is important for IL-3 mediated cell survival but not proliferation." Cell survival and proliferation are cellular activities encompassed by claim 21. 14-3-3 binding

is associated with cellular survival but not proliferation. Therefore, using IL-3 to activate proliferation is an inoperative embodiment because phosphorylation of the β_c chain binding motif is not required for proliferation.

The claims also encompass a method of activating cell survival of hematopoietic cells comprising "a functional equivalent or analogue" of the β_c chain. Functional equivalents or analogues include variants, i.e. substitutions, deletions or insertions in the β_c chain. Applicant has not provided sufficient guidance as to how to make and use variant β_c chains that are not 100% identical to a wild type β_c chain, but which still retain the desired property of activating cell survival. While Applicant has taught that mutation of several residues between 582 and 587 results in loss of cell survival, Applicant has not taught what residues in the β_c chain can be mutated and retain cell survival. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the sequence where such substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and/or receptor oligomerization. These regions can tolerate only relatively conservative substitutions or no substitutions [see Wells (18 September 1990) "Additivity of Mutational Effects in Proteins." Biochemistry **29**(37): 8509-8517; Ngo *et al.* (2 March 1995) "The Protein Folding Problem and Tertiary Structure Prediction, Chapter 14: Computational Complexity Protein Structure Prediction, and the Levinthal Paradox" pp. 492-495]. Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions.

Due to the large quantity of experimentation necessary to test each combination of cell type/receptor type/cellular activity type to determine whether or not it is operative, the lack of direction/guidance presented in the specification regarding operative embodiments, the limited number of working examples directed to same, the complex

nature of the invention, the state of the prior art which establishes unpredictability in whether or not embodiments will be operative, and the breadth of the claims which fail to recite any limitations to operative embodiments, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 112, 1st paragraph, written description

Claims 21, 22, and 24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. § 112, paragraph 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

In making a determination of whether the application complies with the written description requirement of 35 U.S.C. 112, first paragraph, it is necessary to understand what Applicants are claiming and what Applicants have possession of. Claims 21, 22 and 24 are genus claims because the claims are directed to methods of activating cellular activities that encompass numerous species of cells, species of receptors, and species of cellular activities. The claims encompass any type of cell such as bacteria, yeast, plant or animal. The claims also encompass any receptor with a binding motif comprising a serine, including variants encompassing any number of changes to the amino acid sequence. The specification identifies 22 receptors with such a motif (and no variants) but does not limit the invention to these. The claims also encompass activation of any type of cellular activity. The specification identifies 11 types of activities but does not limit the invention to these. Therefore, each genus is highly variant because a significant number of different species are permitted in any combination. The specification describes a method comprising hematopoietic cells, one particular receptor subunit (the β_c chain shared by the GM-CSF/IL-5/IL-3 receptors) and the activity of cell

survival. Thus, Applicants have possession of a single method of a claimed genus that is highly variant. This single example fails to describe the entire genus of methods that are encompassed by these claims.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. In the instant case, the specification fails to provide sufficient descriptive information, such as what combinations of cell types, receptors, and cellular activities can be used in the claimed method. Features of the cells, receptors, and activities that could distinguish those combinations that produce methods that do not fall within the claimed e genus from those that do are missing from the disclosure. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Furthermore, the prior art does not provide compensatory teachings sufficient to allow one of skill to identify the methods encompassed. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus of methods. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicants were not in possession of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). As discussed above, the skilled artisan cannot envision the encompassed genus of methods, and

therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention and reference to determining whether the method is operative. The method itself is required. See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

Therefore, only a method of activating cellular survival in hematopoietic cells that express a wild type β_c chain, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 21, 22, and 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 21, 22 and 24 are indefinite because it is unclear how the method steps reach the goal required by the preamble. Clarity could be added to the claim by adding at the end a phrase such as, "wherein the cellular activities are activated by _____ (e.g., association of said cytoplasmic protein with said binding motif)" Note that there must be basis in the specification for the concluding statement and the suggestions made by the examiner do not necessarily have basis but are intended to present the general idea of concepts that may be suitable.

Claim 21 is also indefinite because it is not clear what is meant the term "associated with" in the phrase "...the cytoplasmic protein is associated with cellular activities." The specification does not define the term and if associated means that the

protein is required for the cellular activities or if associated means that the protein is just located in the same cell as the cellular activity.

Claim 22 is also indefinite because the method steps do not achieve the goal required by the preamble. The preamble states that the method is "a method of regulating cellular activities". However, the method steps result in activation of a "cell signaling pathway". The specification does not indicate that the terms "cellular activities" and "cell signaling pathway" are identical, and because the terms are different, it is presumed that the terms have different meanings. Therefore, the activating a cell signaling pathway does not meet the goal of regulating cellular activities.

Claim 23 recites the limitation "the cellular activities or cell signaling pathways" in lines 1-2. There is insufficient antecedent basis for the limitation "cell signaling pathways" in the claim. Claim 23 depends from claim 21. Claim 21 recites "cellular activities" but does not recite "cell signaling pathways", and therefore this term as used in claim 23 lacks antecedent basis.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 21, 22 and 24 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Okuda et al, 1997. Blood. 90(12): 4759-4766.

Claim 21 encompasses a method comprising 1) regulating the activation of phosphorylation of a receptor with a binding motif comprising a serine; and 2) subjecting the binding motif to a cytoplasmic protein associated with a cellular activity. Claim 22 encompass a method comprising the same steps 1) and 2) and also 3) activating a cell signaling pathway by interacting the bound cytoplasmic protein with a signaling

molecule involved in the pathway. Claim 24 depends from claim 21 and encompasses the cellular activity of cell survival.

Okuda teaches (page 4763) a method of stimulating cell survival of Ba/F3 cells expressing GMFβ-F8 mutant receptors. This method comprises contacting the cells with GM-CSF. The instant application teaches (for example, see page 40) that contacting cells expressing a β_c chain with GM-CSF stimulates phosphorylation of the binding motif containing Ser-585 and causes a 14-3-3 protein to bind this motif and stimulate cell survival. Therefore, the method of Okuda inherently meets all of the limitations of claims 21, 22, and 24. The fact that Okuda did not appreciate these processes were occurring does not make the method of claims 21, 22, and 24 patentably distinct from the method taught by Okuda.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 571-272-0829. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

ROBERT S. LANDSMAN, PH.D.
PRIMARY EXAMINER

zch